

## TENT COOPERATION TRE /

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 15 March 2000 (15.03.00)	
<b>International application No.</b> PCT/EP99/05331	<b>Applicant's or agent's file reference</b> O/98394 WO
<b>International filing date</b> (day/month/year) 19 July 1999 (19.07.99)	<b>Priority date</b> (day/month/year) 23 July 1998 (23.07.98)
<b>Applicant</b> MILTENBURG, Andreas, Martinus, Maria et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
14 February 2000 (14.02.00)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
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1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Nestor Santesso

Telephone No.: (41-22) 338.83.38

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference O/98394 WO	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/05331	International filing date (day/month/year) 19/07/1999	Priority date (day/month/year) 23/07/1998
International Patent Classification (IPC) or national classification and IPC A61K38/17		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14/02/2000	Date of completion of this report 02 10 2000
Name and mailing address of the international preliminary examining authority  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx 523656 epmu d Fax +49 89 2399 - 4465	Authorized officer Fayos. C  Telephone No +49 89 2399 2180

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05331

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-16 as originally filed

### Claims, No.:

1-3 as originally filed

### Drawings, sheets:

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/05331

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	-
	No	Claims	1-3
Inventive step (IS)	Yes:	Claims	-
	No	Claims	1-3
Industrial applicability (IA)	Yes:	Claims	1-3
	No	Claims	-

2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP99/05331

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1- Reference is made to the following documents:

- D1: WO 96 13517 A (AKZO NOBEL) 9 May 1996 (1996-05-09) cited in the application
- D2: VERHEIJDEN G F ET AL: 'Human cartilage glycoprotein -39 as a candidate autoantigen in rheumatoid arthritis.' ARTHRITIS AND RHEUMATISM, (1997 JUN) 40 (6) 1115-25, XP002089334 cited in the application
- D3: WO 97 40149 A (AKZO NOBEL) 30 October 1997 (1997-10-30)

**NOVELTY - Art. 33 (1) and (2) PCT**

2- **Claims 1-3 are not new for the following reasons:**

- 2.1- D1 relates to (e. g. claim 1 and p 5 lines 19-23) peptides derived from the autoantigen HC gp-39, said peptides comprising at least one of the amino acid sequences FGRSFTLAS, FTLASSETG, YDDQESVKS and FSKIASNTQ. The peptides resemble MHC Class II restricted T-cell epitopes present on the autoantigen HC gp-39 in articular cartilage. HC gp-39 and said peptides can be used in antigen-specific treatment of articular cartilage destruction in autoimmune diseases to induce tolerance of the immune system. D1 furthermore relates to pharmaceutical compositions comprising said autoantigen and/or said peptides. Finally, claim 10 discloses the use of HC gp-39 protein or one or more of the aforementioned peptides for the manufacture of a pharmaceutical preparation for the induction of specific T cell tolerance to the HC gp-39 autoantigen in patients suffering from arthritis, more specifically rheumatoid arthritis, which implicitly includes the use of said peptides for preventing the referred diseases.

Therefore, in the light of D1, claims 1-3 are not new.

2.2- D2 discloses the identification of HC gp-39 as a candidate for antigen-specific immunotherapy. Moreover, as mentioned on p 1124 § 1 and 3, inhalation of HC gp-39 by the patients led to immunologic nonresponsiveness, i. e. tolerization of specific T cells, and to suppression of HC gp-39 induced arthritis. Therefore HC gp-39 is a recognised candidate for antigen-specific therapy in reumathoid arthritis.

Therefore, D2 destroys the novelty of claims 1 and 3.

2.3- D3 discloses (e. g. claim 5 and p 6 lines 5-13) the use of autoantigen HC gp-39, and proteins comprising an amino acid sequence which exhibits at least 50 % homology with the amino acid sequence of HC gp-39, in antigen-specific treatment of articular cartilage destruction in autoimmune diseases in mammals to induce systemic tolerance of the immune system. D3 (e. g. claim 3) furthermore relates to pharmaceutical compositions comprising said autoantigen and/or said arthritogenic proteins.

Therefore, D3 destroys the novelty of claims 1 and 3.

2.4- Note that the discovery that HC gp-39, and fragments thereof, exert their therapeutic effect (i. e. prevention of inflammatory diseases) by modulating the reactivity of lymphocytes that are reactive to antigens other than HC gp-39, does not render the referred therapeutic effect novel.

2.5- Hence, claims 1-3 are not new.

#### **INVENTIVE STEP - Art. 33 (1) and (3) PCT**

3- The subject matter of claims 1-3, which is not new, is also not inventive.

4- **That part of the subject matter of claim 2 which is formally new over the prior**

**art cited (i. e. the claimed use as far as the amino acid sequences corresponding to SEQ ID NO: 4-8 are concerned), does not involve an inventive step over D2 and D3 (see below):**

- 4.1- D2 discloses that the following HC gp-39 derived peptides were synthesised SQRFSKIASNTQSR, PTFGRSFTLASSE, RSFTLASSETGVG, VGYDDQESVKSKV (table 3 p 1118) and tested for their capacity to induce proliferative responses in PBMC from rheumatoid arthritis patients, i. e. to bind to DR4 molecules (p 1119 § 3). Since immune responses were induced, T cell epitopes within CH gp-39 were thereby identified (p 1123 §3).

Hence, D2 strongly suggests the use of HC gp-39 fragments such as SQRFSKIASNTQSR, PTFGRSFTLASSE, RSFTLASSETGVG, VGYDDQESVKSKV in the same way as the related protein HC gp-39 from which they are derived (i. e. to prevent inflammatory diseases or rheumatoid arthritis by tolerization).

- 4.2- D3 also suggests the use of homologous sequences of HC gp-39 for treating autoimmune diseases (see item 3.3- above).
- 4.3- Therefore, the subject matter of claim 2 which is formally new over the prior art cited (i. e. the claimed use as far as the amino acid sequences corresponding to SEQ ID NO: 4-8 are concerned) is not inventive.

#### **INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT**

- 5- Claims 1-3 appear to be industrially applicable**

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/05331

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 805 206 A (SMITHKLINE BEECHAM CORPORATION) 5 November 1997 (1997-11-05) the whole document	1, 3
X	VERHEIJDEN G F ET AL: "Human cartilage glycoprotein -39 as a candidate autoantigen in rheumatoid arthritis." ARTHRITIS AND RHEUMATISM, (1997 JUN) 40 (6) 1115-25, XP002089334 cited in the application the whole document	1, 3
A	EP 0 823 478 A (SMITHKLINE BEECHAM CORPORATION) 11 February 1998 (1998-02-11) the whole document	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 March 2000

Date of mailing of the international search report

04/04/2000

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
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Fax: (+31-70) 340-3016

Authorized officer

Moreau, J



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/05331

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim No.
Category	Citation of document, with indication, where appropriate, of the relevant passages	
A	WO 96 13517 A (AKZO NOBEL) 9 May 1996 (1996-05-09) cited in the application the whole document ----	1-3
X	WO 97 40149 A (AKZO NOBEL) 30 October 1997 (1997-10-30) page 4 -page 6 ----	1,3
P,X	COENEN DE ROO C J J ET AL: "Human cartilage GP-39 induces and modifies a chronic relapsing arthritis in mice." 62ND NATIONAL SCIENTIFIC MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY AND THE 33RD NATIONAL SCIENTIFIC MEETING OF THE ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS; SAN DIEGO, CALIFORNIA, USA; NOVEMBER 8-12, 1998, vol. 41, no. 9 SUPPL., 1998, page S214 XP002133815 Arthritis & Rheumatism Sept., 1998 ISSN: 0004-3591 the whole document -----	1-3

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/05331

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 805206	A	05-11-1997	JP 10066585 A	10-03-1998
EP 823478	A	11-02-1998	US 5811535 A	22-09-1998
			JP 10179170 A	07-07-1998
WO 9613517	A	09-05-1996	AT 177756 T	15-04-1999
			AU 696827 B	17-09-1998
			AU 3925295 A	23-05-1996
			BR 9506377 A	16-09-1997
			CN 1168677 A	24-12-1997
			DE 69508380 D	22-04-1999
			DE 69508380 T	09-09-1999
			EP 0733065 A	25-09-1996
			ES 2130672 T	01-07-1999
			FI 962619 A	25-06-1996
			GR 3030296 T	30-09-1999
			HU 74847 A	28-02-1997
			JP 9507861 T	12-08-1997
			NO 962695 A	26-06-1996
			NZ 295659 A	26-02-1998
			PL 315198 A	14-10-1996
			TR 960361 A	21-06-1996
			US 5736507 A	07-04-1998
WO 9740149	A	30-10-1997	US 5843449 A	01-12-1998
			AU 2386997 A	12-11-1997
			BR 9708714 A	03-08-1999
			CA 2251584 A	30-10-1997
			CN 1216582 A	12-05-1999
			CZ 9803333 A	17-03-1999
			EP 0904369 A	31-03-1999
			NO 984835 A	16-12-1998
			PL 329350 A	29-03-1999

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>0/98394 WO</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 99/05331</b>	International filing date (day/month/year) <b>19/07/1999</b>	(Earliest) Priority Date (day/month/year) <b>23/07/1998</b>
Applicant <b>AKZO NOBEL N.V. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

National Application No  
PCT/EP 99/05331

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 805 206 A (SMITHKLINE BEECHAM CORPORATION) 5 November 1997 (1997-11-05) the whole document ---	1,3
X	VERHEIJDEN G F ET AL: "Human cartilage glycoprotein -39 as a candidate autoantigen in rheumatoid arthritis." ARTHRITIS AND RHEUMATISM, (1997 JUN) 40 (6) 1115-25, XP002089334 cited in the application the whole document ---	1,3
A	EP 0 823 478 A (SMITHKLINE BEECHAM CORPORATION) 11 February 1998 (1998-02-11) the whole document --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

23 March 2000

Date of mailing of the international search report

04/04/2000

Name and mailing address of the ISA

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Authorized officer

Moreau, J

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/05331

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 13517 A (AKZO NOBEL) 9 May 1996 (1996-05-09) cited in the application the whole document ---	1-3
X	WO 97 40149 A (AKZO NOBEL) 30 October 1997 (1997-10-30) page 4 -page 6 ---	1,3
P,X	COENEN DE ROO C J J ET AL: "Human cartilage GP-39 induces and modifies a chronic relapsing arthritis in mice." 62ND NATIONAL SCIENTIFIC MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY AND THE 33RD NATIONAL SCIENTIFIC MEETING OF THE ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS; SAN DIEGO, CALIFORNIA, USA; NOVEMBER 8-12, 1998, vol. 41, no. 9 SUPPL., 1998, page S214 XP002133815 Arthritis & Rheumatism Sept., 1998 ISSN: 0004-3591 the whole document -----	1-3

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/05331

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 805206	A	05-11-1997	JP	10066585 A	10-03-1998
EP 823478	A	11-02-1998	US	5811535 A	22-09-1998
			JP	10179170 A	07-07-1998
WO 9613517	A	09-05-1996	AT	177756 T	15-04-1999
			AU	696827 B	17-09-1998
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			BR	9506377 A	16-09-1997
			CN	1168677 A	24-12-1997
			DE	69508380 D	22-04-1999
			DE	69508380 T	09-09-1999
			EP	0733065 A	25-09-1996
			ES	2130672 T	01-07-1999
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			HU	74847 A	28-02-1997
			JP	9507861 T	12-08-1997
			NO	962695 A	26-06-1996
			NZ	295659 A	26-02-1998
			PL	315198 A	14-10-1996
			TR	960361 A	21-06-1996
			US	5736507 A	07-04-1998
WO 9740149	A	30-10-1997	US	5843449 A	01-12-1998
			AU	2386997 A	12-11-1997
			BR	9708714 A	03-08-1999
			CA	2251584 A	30-10-1997
			CN	1216582 A	12-05-1999
			CZ	9803333 A	17-03-1999
			EP	0904369 A	31-03-1999
			NO	984835 A	16-12-1998
			PL	329350 A	29-03-1999